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Epoxygenase Eicosanoids: Synthesis of Tetrahydrofuran-Diol Metabolites and Their Vasoactivity

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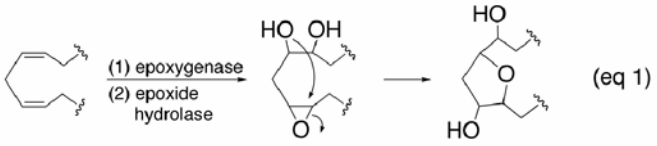
Abstract

Eight members of a recently identified family of tetrahydrofuran-diols (THFDs), originating from epoxyeicosatrienoic acids (EETs), were prepared stereospecifically from D-(+)-glucose. The THFDs potently induced relaxation of pre-contracted bovine arteries.

Arachidonic acid is metabolized by the cytochrome P450 epoxygenase pathway into four regioisomeric epoxyeicosatrienoic acids (EETs),[1] whose varied contributions to homeostasis and pathophysiology have attracted considerable attention.[2] Secondary metabolism results in even greater structural diversity by converting the EETs into vic-diols,[3] S-glutathione adducts,[4] or more highly oxygenated products[5] including a family of bioactive tetrahydrofuran-diols (THFDs).[6–8] It is unclear, at present, if the THFDs originate from completely enzymatic processes[9] or from spontaneous, nonenzymatic epoxide annulations (e.g., eq 1).[10] To expedite current structural and pharmacological investigations, we report herein the synthesis of eight isomers of defined stereochemistry starting from an inexpensive member of the chiral pool and their evaluations as vasomodulators. A structurally similar, but biosynthetically distinct class of endogenous arachidonate tetrahydrofuran-diols,[11] known collectively as isofurans,[12] has also been described and representative members prepared by chemical synthesis.[13]



(eq 1)

Since the “mid-chain” THFDs, i.e., those derived from transannular cyclizations between epoxides at the original $\Delta^{8,9}$- and $\Delta^{11,12}$-olefins, were found to be the most efficacious for increasing intracellular free Ca^{2+} in rat pulmonary alveolar cells,[6b] our initial synthetic efforts focused on this system. Our strategy (Scheme 1) utilized furanoside **1**,[14] readily obtained from D-(+)-glucose, as a convenient starting point.[15] Alkynylation of **1** using the dianion of commercial 5-hexynoic acid and esterification of the adduct with diazomethane provided the known homopropargylic alcohol **2**.[14] Benzoylation of **2** followed by reductive allylation at the anomeric center induced with $BF_3{\cdot}Et_2O$ according to the method of García-Tellado[16] afforded a chromatographically separable mixture (5:1) of **3** and its α-isomer **4** in good combined yield.[17] Sequential silylation of the newly liberated alcohol, OsO_4 dihydroxylation

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of the terminal olefin, and cleavage of the resultant *vic*-diol converted **3** into the somewhat labile aldehyde **5** which was immediately subjected to Wittig *cis*-olefination using *n*-hexylidenetriphenylphosphorane in a non-polar solvent to minimize β-elimination. Semi-hydrogenation of the acetylene over P-2 nickel[18] and fluoride-induced desilylation gave **6**. Saponification of the esters in **6** delivered 8(*R*),9(*S*),11(*R*),12(*S*)-THFD (**7**) without incident whereas Mitsunobu inversion[19] at C(11) prior to saponification led to 8(*R*),9(*S*),11(*S*),12(*S*)-THFD (**8**).

An analogous series of transformations as described in Scheme 1, when applied to α-isomer **4**, yielded 8(*R*),9(*S*),11(*R*),12(*R*)-THFD (**10**) and 8(*R*),9(*S*),11(*S*),12(*R*)-THFD (**11**) by way of methyl ester **9** (Scheme 2).

Regrettably, all attempts to access the 8(*S*)-series of THFDs via Mitsunobu inversion[19] of alcohol **2** or the derived 5(*Z*)-olefin were discouraged by a facile dehydration. Only minor amounts of the desired 8(*S*)-ester could be obtained. Oxidation/reduction sequences through the corresponding ketone as a means of establishing the *S*-alcohol were also stymied by poor yields and/or migration of the adjacent olefin. Consequently, the known[20] epimeric epoxide **12** (Scheme 3) was used to prepare benzoates **13** and **17** following the now well-established protocols from Scheme 1. After chromatographic separation, **13** and **17** were elaborated into **14** and **18**, respectively. In turn, these intermediates were advanced to 8(*S*),9(*S*),11(*R*),12(*S*)-THFD (**15**)/8(*S*),9(*S*),11(*S*),12(*S*)-THFD (**16**) and 8(*S*),9(*S*),11(*R*),12(*R*)-THFD (**19**)/8(*S*),9(*S*),11(*S*),12(*R*)-THFD (**20**), accordingly.

The THFDs were tested for vasodilatory activity using bovine coronary arteries preconstricted with the thromboxane-mimetic U-46619 (10–20 nM).[21] All caused relaxation of the arteries when used from 10^{-8}–10^{-5} M (Figure 1A and 1B). In the same assay, the endogenous dilator 14,15-epoxyeicosatrienoic acid (14,15-EET) also relaxed coronary arteries over a similar concentration range.[22] Notably, THFD **10** (ED_{50} = 3.0 ± 0.11μM) and 14,15-EET (ED_{50} = 2.5 ± 0.10μM) were equally active while the other THFDs were less efficacious. These studies indicate that, in this series, a *trans*-tetrahydrofuran skeleton and 11(*R*)-hydroxyl are necessary for full agonist activity with respect to the parent EETs. The physiological significance of these secondary metabolites and their utility as EET mimetics are under investigation and the results will be published in due course.

Acknowledgements

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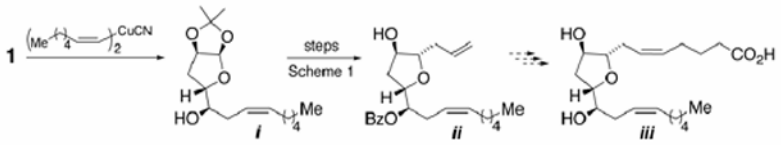
15. As proof of principle that our strategy could be used to prepare other members of this family, e.g., *iii*, 1-(*Z*)-heptene cuprate was added to epoxide 1 to give *i* which ultimately evolved *ii* following the procedures in Scheme 1.



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17. Compound **3**: TLC, EtOAc/hexane (1:1), R_f ~ 0.40; $[\alpha]^D_{23}$ - 34.2 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.74 (apparent p, J ~ 7.2 Hz, 2H), 1.91 (bs, 1H), 2.01 (ddd, J ~ 3.2, 6.4, 13.2 Hz, 1H), 2.11–2.23 (m, 5H), 2.37 (t, 2H, J ~ 7.6 Hz), 2.60–2.70 (m, 2H), 3.64 (s, 3H), 3.87 (td, J ~ 3.2, 6.4 Hz, 1H), 4.15 (t, J ~ 2.4 Hz, 1H), 4.70 (dt, J ~ 6.0, 6.4 Hz, 1H), 4.99–5.06 (m, 2H), 5.24 (apparent q, J ~ 6.0 Hz, 1H), 5.70–5.82 (m, 1H), 7.42 (apparent t, J ~ 7.6 Hz, 2H), 7.54–7.60 (tt, J ~ 1.2, 7.2 Hz, 1H), 8.03–8.06 (dd, J ~ 1.2, 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.20, 21.79, 23.97, 32.82, 36.23, 38.51, 51.64, 73.54, 75.04, 75.94, 78.06, 81.34, 85.95, 117.51, 128.47, 129.73, 130.17, 133.18, 134.09, 165.82, 173.93. TBDMS ether of **3**: TLC, MeOH/CH_2Cl_2 (1:1), R_f ~ 0.87; [a]$^D_{23}$ -24.1 (*c* 0.87, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.83 (s, 9H), 1.68 (apparent p, J ~ 7.2 Hz, 2H), 1.85 (ddd, J ~ 3.6, 5.2, 12.8 Hz, 1H), 1.98–2.21 (m, 5H), 2.30 (t, J ~ 7.6 Hz, 2H), 2.51–2.63 (m, 2H), 3.59 (s, 3H), 3.74 (dt, J ~ 4.0, 6.4 Hz, 1H), 4.00 (dt, J ~ 3.6, 7.2 Hz, 1H),

4.37 (dt, J ~ 6.4, 8.0 Hz, 1H), 4.80–4.97 (m, 2H), 5.19 (apparent q, J ~ 6.0 Hz, 1H,), 5.63–5.74 (m, 1H), 7.45 (apparent t, J ~ 8.0 Hz, 2H), 7.57 (apparent t, J ~ 7.2 Hz, 1H), 8.02–8.05 (apparent dd, J ~ 1.6, 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ-4.58, −4.41, 18.08, 18.29, 21.82, 24.06, 25.90, 32.84, 36.62, 38.18, 51.60, 73.76, 75.25, 76.02, 78.11, 81.35, 85.87, 117.35, 128.49, 129.83, 130.39, 133.15, 134.36, 165.80, 173.74. Compound **4**: $[\alpha]^{D}_{23}$ -19.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (apparent p, J ~ 7.2 Hz, 2H), 2.02 (ddd, J ~ 1.6, 6.8, 13.2 Hz, 1H), 2.09 (td, J ~ 4.4, 8.4 Hz, 1H), 2.14–2.19 (m, 2H), 2.28–2.43 (m, 4H), 2.57–2.70 (m, 2H), 3.64 (s, 3H), 3.85 (td, J ~ 2.8, 6.4 Hz, 1H), 4.30 (br s, 1H), 4.50 (dt, J ~ 6.0, 8.8 Hz, 1H), 5.01–5.12 (m, 2H), 5.24 (q, J ~ 6.0 Hz, 1H,),5.78–5,81 (m, 1H), 7.45 (apparent t, J ~ 7.6 Hz, 2H), 7.57 (apparent tt, J ~ 1.2, 7.2 Hz, 1H), 8.02–8.05 (apparent dd, J ~ 1.2, 7.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.92, 24.09, 25.94, 32.88, 33.99, 37.80, 51.64, 73.30, 74.16, 76.08, 77.66, 81.32, 83.33, 116.67, 128.54, 129.85, 130.42, 133.18, 135.40, 165.95, 173.79. Compound **6**: TLC, EtOAc/hexane (1:4), R_f ~ 0.40; $[\alpha]^{D}_{23}$ -23.0 (*c* 1.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J ~ 7.2 Hz, 3H), 1.16–1.32 (m, 6H), 1.61–1.72 (m, 3H), 1.88–1.98 (m, 4H), 2.03–2.24 (m, 5H), 2.28 (t, J ~ 7.2 Hz, 2H), 2.41–2.55 (m, 2H), 3.65 (s, 3H), 3.76–3.81 (m, 1H), 4.10 (dt, J ~ 2.8, 5.6 Hz, 1H), 4.31 (dt, J ~ 6.0, 8.8 Hz, 1H), 5.27–5.51 (m, 5H), 7.44 (apparent t, J ~ 7.6 Hz, 2H), 7.56 (apparent t, J ~ 7.6 Hz, 1H), 8.01–8.04 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.25, 22.74, 24.84, 26.86, 27.52, 29.39, 29.58, 31.64, 32.12, 33.62, 36.16, 51.71, 74.88, 75.51, 78.67, 86.48, 124.24, 125.04, 128.56, 129.79, 130.53, 131.93, 133.02, 133.15, 166.02, 174.29. Compound **7**: TLC, EtOAc, R_f 0.18; $[\alpha]^{D}_{23}$ -26.5 (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J ~ 6.8 Hz, 3H), 1.22–1.39 (m, 6H), 1.70 (q, J ~ 7.2 Hz, 2H), 1.78 (ddd, J ~ 4.0, 6.0, 13.2 Hz, 1H), 2.03 (apparent q, J ~ 7.2 Hz, 2H), 2.08–2.16 (m, 3H), 2.17– 2.24 (m, 2H), 2.28 (t, J ~ 7.2 Hz, 2H), 2.35 (t, J ~ 7.2 Hz, 2H), 3.82–3.86 (m, 2H), 4.09–4.16 (m, 2H), 5.35–5.57 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.26, 22.75, 24.65, 26.66, 27.63, 29.43, 31.02, 31.70, 31.96, 33.52, 33.76, 71.51, 75.73, 80.85, 86.31, 124.23, 126.32, 131.39, 133.41, 178.83; MS (AP-LC) *m/z* 354 (M^+, 100 %). Compound **8**: TLC, EtOAc, R_f ~ 0.29; $[\alpha]^{D}_{23}$ 15.3 (*c* 0.96, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J ~ 6.8 Hz, 3H), 1.24– 1.40 (m, 6H), 1.65–1.78 (m, 2H), 2.00 (dd, J ~ 3.2, 12.8 Hz, 1H), 2.04–2.26 (m, 7H), 2.34 (t, J ~ 7.2 Hz, 2H), 2.38–2.51 (m, 2H), 3.61(td, J ~ 2.4, 7.2 Hz, 1H), 3.88 (apparent t, J ~ 6.4 Hz, 1H), 5.40–5.55 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.27, 22.79, 24.65, 26.66, 27.17, 27.55, 29.50, 31.73, 31.94, 33.46, 34.31, 71.21, 72.01, 80.07, 83.77, 125.12, 125.93, 132.21, 132.71, 178.56; MS (AP-LC) *m/z* 354 (M^+, 100 %). Compound **9**: TLC, EtOAc/hexane (1:1), R_f ~ 0.52; $[\alpha]^{D}_{23}$ -26.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J ~ 10.0 Hz, 3H), 1.19–1.39 (m, 6H), 1.59–1.70 (m, 4H), 2.00–2.20 (m, 6H), 2.27 (t, J ~ 10.0 Hz, 2H), 2.31–2.58 (m, 4H), 3.64 (s, 3H), 3.82–3.86 (m, 1H), 4.30 (br s, 1H), 4.41 (dt, J ~ 9.2, 12.0 Hz, 1H), 5.24 (dt, J ~ 7.2, 9.2 Hz, 1H), 5.29–5.53 (m, 5H), 7.41–7.46 (m, 2H), 7.52–7.57 (m, 1H), 7.99–8.03 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.22, 22.70, 24.81, 26.81, 27.44, 27.56, 29.36, 29.53, 31.65, 33.57, 37.35, 51.67, 72.97, 75.61, 77.86, 83.01, 124.55, 125.01, 128.56, 129.76, 130.45, 131.89, 132.90, 133.15, 166.09, 174.24. Compound **10**: TLC, MeOH/CH_2Cl_2 (1:9), R_f ~ 0.28; $[\alpha]^{D}_{23}$ -12.4 (*c* 1.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J ~ 6.8 Hz, 3H), 1.22–1.40 (m, 8H), 1.71 (apparent p, J ~ 7.2 Hz, 2H), 1.93 (dd, J ~ 6.0, 13.2 Hz, 1H), 2.24–2.22 (m, 7H), 2.35 (t, J ~ 7.2 Hz, 2H), 2.38–2.49 (m, 2H), 3.84–3.94 (m, 2H), 4.19–4.24 (m, 1H), 4.33 (t, J ~ 3.2 Hz, 1H), 5.36–5.55 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.25, 22.75, 24.71, 26.71, 27.59, 29.44, 29.88, 31.01, 31.70, 33.65, 34.78, 72.33, 73.05, 80.09, 83.42, 124.65, 126.33, 131.48, 132.95, 179.00; MS (AP-LC) *m/z* 354 (M^+, 100 %). Compound **11**: TLC, MeOH/CH_2Cl_2 (1:9), R_f ~ 0.29; $[\alpha]^{D}_{23}$ 16.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J ~ 6.8 Hz, 3H), 1.22–1.40 (m, 7H), 1.62–1.78 (m, 2H) 1.92–2.30 (m, 10H), 2.35 (t, J ~ 6.8 Hz, 2H), 3.85–3.90 (m, 1H), 4.03 (t, J ~ 7.2 Hz, 1H), 4.07 (d, J ~ 5.6 Hz, 1H), 4.15 (dt, J ~ 2.8, 9.2 Hz, 1H), 5.34–5.55 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.25, 22.74, 24.66, 26.68, 27.58, 29.42, 31.31, 31.69, 31.89, 32.82, 33.60, 72.20, 74.48, 80.54, 87.13, 124.47, 125.99, 131.89, 132.88, 178.69; MS (AP-LC) *m/z* 354 (M^+, 100 %). Compound **13**: TLC, 3% MeOH/CH_2Cl_2, R_f ~ 0.26; $[\alpha]^{D}_{23}$ 1.1 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68 (s, 1H), 1.75 (apparent p, J ~ 7.2 Hz, 2H), 1.90–2.00 (m, 3H), 2.16–2.21 (m, 2H), 2.33– 2.41 (m, 3H), 2.59–2.74 (m, 2H), 3.65 (s, 3H), 3.86 (td, J ~ 2.8, 6.4 Hz, 1H), 4.12 (apparent q, J ~ 2.8 Hz, 1H), 4.70 (td, J ~ 4.0, 8.4 Hz, 1H), 5.07–5.14 (m, 2H), 5.19 (td, J ~ 4.0, 6.8 Hz, 1H), 5.82–5.94 (m, 1H), 7.42 (apparent t, J ~ 7.6 Hz, 2H), 7.55–7.60 (m, 1H), 8.06–8.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.32, 21.81, 24.07, 32.95, 36.51, 38.64, 51.76, 73.58, 75.28, 76.24, 77.47, 81.38, 85.85, 117.62, 128.57, 129.94, 130.17, 133.29, 134.38, 166.17, 174.00. Compound **14**: $[\alpha]^{D}_{23}$ 11.9 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J ~ 7.1 Hz, 3H), 1.16–1.38 (m, 6H), 1.65 (quintet, J ~ 7.3 Hz, 2H), 1.88–2.18(m, 6H), 2.23–2.41 (m, 4H), 2.54 (t, J ~ 6.3, Hz, 2H), 3.65 (s, 3H), 3.81

(ddd, J ~ 3.2, 6.2, 7.6 Hz, 1H), 4.05–4.09 (m, 1H), 4.37 (dt, J ~ 3.9, 7.0 Hz, 1H), 5.17 (dt, J ~ 3.9, 6.6 Hz, 1H), 5.40–5.56 (m, 4H), 7.40–7.47 (m, 2H), 7.53–7.60 (m, 1H), 8.04–8.08 (m, 2H); ^{13}C NMR (75 MHz, $CDC1_3$) δ 14.23, 22.73, 24.84, 26.81, 27.63, 29.45, 29.54, 31.67, 32.18, 33.63, 36.57, 51.69, 74.79, 75.46, 77.98, 86.26, 124.49, 125.20, 128.56, 129.91, 130.38, 132.08, 132.93, 133.18, 166.36, 174.31. Compound **15**: $[\alpha]^D_{23}$ -10.0 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J ~ 7.0 Hz, 3H), 1.24–1.40 (m, 6H), 1.70 (quintet, J ~ 7.0 Hz, 2H), 1.85 (apparent ddd, J ~ 2.8, 5.9, 13.1 Hz, 1H), 1.93–2.06 (m, 3H), 2.12 (apparent q, J ~ 5.7 Hz, 2H), 2.22–2.30 (m, 4H), 2.36 (t, J ~ 7.3 Hz, 2H), 3.47 (apparent q, J ~ 6.1 Hz, 1H), 3.83 (dt, J ~ 10.4, 3.0 Hz, 1H), 4.04–4.13 (m 2H), 5.36–5.56 (m, 4H); ^{13}C NMR (75 MHz, $CDC1_3$) δ 14.26, 22.75, 24.57, 26.64, 27.64, 29.43, 31.71, 32.11, 32.22, 33.31, 36.98, 73.72, 75.96, 80.56, 86.14, 124.20, 126.51, 131.23, 133.35, 178.66. Compound **16**: $[\alpha]^D_{23}$ 25.0 (*c* 0.68, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J ~ 6.7 Hz, 3H), 1.25–1.40 (m, 6H), 1.72 (quintet, J ~ 7.4 Hz, 2H), 1.83 (apparent dd, J ~ 14.0, 3.0 Hz, 1H), 2.07 (q, J ~ 7.0 Hz, 2H), 2.14 (q, J ~ 6.7 Hz, 2H), 2.28–2.52 (m, 7H), 3.54 (ddd, J ~ 10.4, 5.5, 2.4 Hz, 1H), 3.65 (dt, J ~ 14.0, 2.8 Hz, 1H), 4.01 (td, J ~ 9.8, 2.8 Hz, 1H), 4.07 (dd, J ~ 5.5, 2.8 Hz, 1H), 5.40–5.55 (m, 4H); ^{13}C NMR (75 MHz, $CDC1_3$) δ 14.28, 22.80, 24.62, 26.66, 27.30, 27.56, 29.55, 31.74, 32.28, 33.35, 38.33, 71.67, 73.51, 78.99, 84.13, 125.25, 126.61, 132.04, 132.62, 178.58. Compound **17**: TLC, 3% MeOH/CH_2Cl_2, R_f ~ 0.32; $[\alpha]^D_{23}$ 10.5 (*c* 0.72, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76–1.78 (m, 3H), 1.97 (ddd, J ~ 4.8, 9.2, 13.6 Hz, 1H), 2.12 (dd, J ~ 6.8, 13.2 Hz, 1H), 2.15–2.21 (m, 2H), 2.33–2.53 (m, 4H), 2.59–2.74 (m, 2H), 3.66 (s, 3H), 3.86 (td, J ~ 2.4, 6.8 Hz, 1H), 4.28 (apparent s, 1H), 4.59–4.64 (m, 1H), 5.07–5.21 (m, 3H), 5.81–5.94 (m, 1H), 7.45 (apparent t, J ~ 7.6 Hz, 2H), 7.55–7.60 (m, 1H), 8.04–8.07 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.37, 21.92, 24.13, 29.91, 32.98, 33.77, 37.54, 51.78, 73.19, 74.34, 76.22, 81.51, 82.50, 117.30, 128.62, 129.97, 130.25, 133.30, 134.76, 166.27, 173.95.

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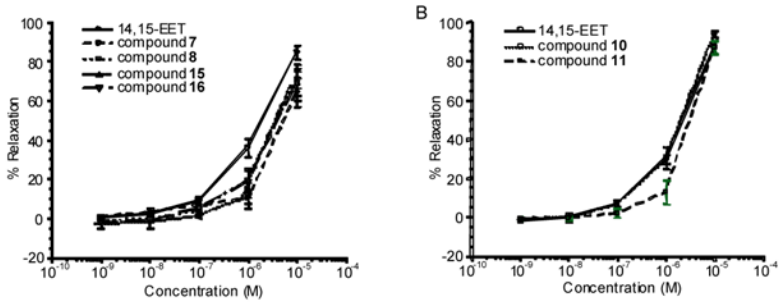
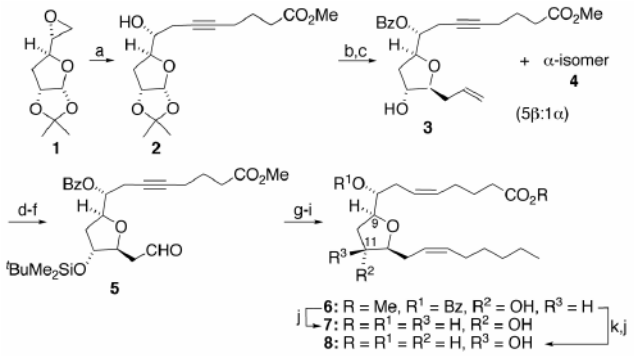
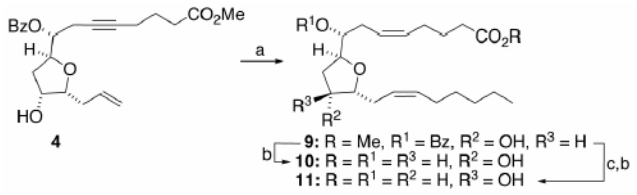


Figure 1.
Relaxation of pre-contracted bovine arteries by THFDs and 14,15-EET.



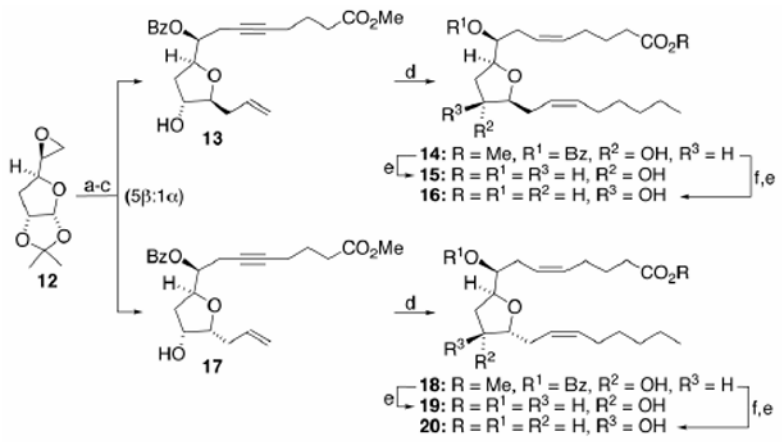
Scheme 1.

Reagents and conditions: (a) 5-hexynoic acid, *n*-BuLi (2 equiv), HMPA, 5°C for 1 h, then 23° C for 12 h; CH_2N_2, 5% MeOH/Et_2O, 23°C, 1 h, 60–65%; (b) PhC(O)Cl, DMAP, Et_3N, CH_2Cl_2, 23°C, 12 h, 97%; (c) $Me_3SiCH_2CH{=}CH_2/BF_3{\cdot}Et_2O$, CH_2Cl_2, 23°C, 18 h, 82% (α-/β-isomers combined); (d) *t*-$BuMe_2SiCl$, ImH, DMF, 50°C, 12 h, 95%; (e) OsO_4 (2 mol %), NMO, *t*-BuOH, 23°C, 12 h; (f) $NaIO_4/SiO_2$, CH_2Cl_2, 23°C, 1.5 h; (g) $H_3C(CH_2)_5PPh_3Br$, NaN$(SiMe_3)_2$, $PhCH_3$/THF (1:1), −90°C for 0.5 h, then warm to 23°C overnight, 70% over three steps; (h) $Ni(OAc)_2$, $NaBH_4$, $(H_2NCH_2)_2$, H_2 (1 atm), EtOH, 23°C, 5 h, 85%; (i) *n*-Bu_4NF, THF, 23°C, 12 h, 70%; (j) LiOH, THF/H_2O (3:1), 92%; (k) DEAD/PPh_3/$PhCO_2H$, THF, 1 h, 0°C, 93%.



Scheme 2.

Reagents and conditions: (a) steps d-i from Scheme 1; (b) LiOH, THF/H_2O (3:1), 23°C, 10 h, 92–96%; (c) DEAD/PPh_3/$PhCO_2H$, THF, 1 h, 0°C, 90–93%.



Scheme 3.

Reagents and conditions: (a) 5-hexynoic acid, *n*-BuLi (2 equiv), HMPA, 5°C for 1 h, then 23° C for 12 h; CH_2N_2, 5% MeOH/Et_2O, 23°C, 1 h, 60–65%; (b) PhC(O)Cl, DMAP, Et_3N, CH_2Cl_2, 23°C, 12 h, 93%; (c) $Me_3SiCH_2CH{=}CH_2/BF_3{\cdot}Et_2O$, CH_2Cl_2, 23°C, 18 h, 80–82% (α-/β-isomers combined); (d) steps d-i in Scheme 1; (e) LiOH, THF/H_2O (3:1), 23°C, 10 h, 92–96%; (f) DEAD/PPh_3/$PhCO_2H$, THF, 1 h, 0°C, 90–93%.